

## **Remarks**

### **Interview Summary**

Applicant thanks the Examiner and his supervisor for the courtesy of an interview conducted Juen 11, 2009. The obviousness rejection under 35 U.S.C. §103 and the underlying cited art references were discussed. Applicant presents the following amendments and remarks for the Examiner's consideration.

### **Amendments to the Claims**

Claim 16 has been amended to recite that the treated mammal suffers from periodontal disease. Support for this amendment is found throughout the specification.

Claim 16 has also been amended to recite that the local administration of GM-CSF occurs injection in the proximity of the periodontal disease. Support for this amendment is found in paragraph [0045] of the present application, published as US 2008-0038222.

Claim 21 has been amended for clarity and to correct a misspelling.

Claims 32-48 have been newly added. Support for claims 32-35 is found in paragraph [0045] of the present application, published as US 2008-0038222. Support for new claims 37-47 is found throughout the specification, for example in paragraphs [0025]-[0027] and [0045] of the present application, published as US 2008-0038222. Support for new claims 36 and 48 is found, for example, in Examples 1 and 2 of the present application, published as US 2008-0038222.

No new matter has been added as a result of the present amendments, each of which is made without prejudice. Applicant reserves the right to pursue any subject matter canceled as a result of the present amendments in future prosecution, either in this application or in one or more continuing applications.

### **Rejections under 35 U.S.C. §103**

Claims 16, 18, and 21-26 were rejected under 35 U.S.C. §103 as being obvious over US Patent No. 5,162,111 to Grabstein *et al.* ("Grabstein *et al.*"), in view of Grzybowski *et al.* (Int. J.

Pharmaceutics 184: 179-187, 1999 (“Grzybowski *et al.*”), and further in view of US Patent No. 4,804,530 to Sampathkumar (“Sampathkumar”). Applicant traverses this rejection.

As an initial matter, Applicant notes that claim 16 has been amended to recite that the local administration of GM-CSF occurs by injection.

The Examiner states that Applicant’s previous arguments were considered but are not persuasive for the reasons set forth on pages 6-10 of the final Office Action mailed December 23, 2008. On page 10 of that Office Action, the Examiner states “...it would had been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Grabstein in view of Grzybowski et al who teach the treatment of bacterial disease using locally administering GM-CSF to incorporate the treatment of gingivitis using the GM-CSF in view of Sampathkumar who teaches the gingivitis is localized bacterial disease as GM-CSF is known to elicit antibacterial effects. One would have been motivated to do so to because gingivitis is known to be a bacterial disease. One would have a reasonable expectation of success in treating a local bacterial disease by locally administering GM-CSF, since the treatment of bacterial disease by administering the GM-CSF to a subject has been known in the art at time the instant invention was made.”

Applicant disagrees that one of ordinary skill in the art would have been motivated to combine the cited references based simply on the fact that gingivitis is a known bacterial disease. Moreover, based on the disclosures of the cited references, one of ordinary skill in the art would have no reasonable expectation of success in treating periodontal disease by locally administering GM-CSF.

#### Motivation to Combine

Grabstein demonstrates that GM-CSF is effective in treating a systemic infection caused by *S. typhimurium* when systemically administered. Grzybowski *et al.* demonstrate only that bandages containing G-CSF can be used in wound healing. Although Grzybowski *et al.* prepare bandages containing GM-CSF and show that the bandages affect *in vitro* phagocytic activity of peripheral blood cells (see page 183, first column), these bandages are never used for wound healing, much less for the treatment of a bacterial infection, and are certainly not used in the treatment of periodontal disease. Based on the information in Grzybowski *et al.*, one of ordinary

skill in the art would not know whether GM-CSF would be effective when locally administered, and given the differences in the route of administration and the different diseases that are treated, would not be motivated to combine the teachings of these two references.

Additionally, Applicant notes that the bacteria treated in Grzybowski *et al.* are aerobic. In contrast, the bacteria causing periodontal disease are anaerobic, see e.g. col. 1, l. 27-28 of Sampathkumar. See also Table 1 of Loesch, *Crit. Rev. Oral Biol. Med.*, 10;245, 1999, a copy of which is submitted with this Request for Continued Examination and cited on the attached information disclosure statement. The vast majority of bacteria in Table 1 are anaerobic, including *Porphyromonas gingivalis*, *Bacteroides forsythus*, *Treponema denticola*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Eubacterium nodatum*, *Selenomonas noxia*, *Porphyromonas gracilis*, *Terponema vincentii*, *Peptostreptococcus micros*, *Eubacterium sp.*, *Selenomonas sp.*, and *Streptococcus intermedius*. The other three bacteria listed in Table 1 are micro-aerophilic. None of the bacteria listed in Table 1 are aerobic. Thus, the anaerobic bacteria involved in periodontal disease are of a fundamentally different type than the single aerobic bacterium exemplified in Grzybowski *et al.*

One of ordinary skill in the art, having knowledge of the teachings of Grabstein, would have no motivation to combine those teachings with the teachings of Grzybowski *et al.* and arrive at the present invention since:

1) There is no mention of anything but the use of GM-CSF for systemic treatment in Grabstein. Also, there is no suggestion in Grabstein of the treatment of periodontal disease. Grzybowski *et al.* disclose a method for treating bacterial wound infections (see e.g., last sentence of abstract), not periodontal diseases. Periodontal disease is not a wound. Indeed, both references are entirely silent regarding periodontal disease. One ordinary skilled in the art would therefore not be motivated to turn to Grzybowski *et al.* when searching for a local treatment of periodontal disease.

2) Even if one ordinary skilled in the art were to consider the teachings of Grabstein and Grzybowski *et al.* together, which is unlikely since neither reference teaches or suggests periodontal disease, he or she would still not be motivated to combine their teachings to arrive at the presently claimed methods. In contrast to the anaerobic bacteria involved in periodontal disease, the bacteria exemplified in Grzybowski *et al.* are aerobic, and would thus be expected to

respond differently to GM-CSF. Applicant reiterates that Grzybowski *et al.* fail to demonstrate that GM-CSF actually has any *in vivo* effect when used for local treatment. Grzybowski *et al.* demonstrate only that GM-CSF extracted from wound dressings has one biological function (see e.g. the first paragraph of Results and discussion section), and exhibits a single effect on one phagocytotic parameter, namely oxygen burst (see Fig. 1 and 2 and e.g. second paragraph in Results and Discussion section). Thus, one of ordinary skill in the art would have no reason to expect that combining the teachings of Grzybowski *et al.* with the systemic administration of Grabstein would result in an effective localized treatment of a bacterial infection, much less the treatment of periodontal disease.

Thus, based on the disparate and incompatible teachings of Grabstein and Grzybowski *et al.* (as well as the incomplete teachings of Grzybowski *et al.*), one of ordinary skill in the art would have no reason to combine these references. Even if the teachings of Grabstein and Grzybowski *et al.* were combined, such a combination would not result in the presently claimed methods since neither reference suggests that GM-CSF could be used in the local treatment of periodontal disease. Indeed, neither Grabstein nor Grzybowski *et al.* teach, suggest, or even contemplate the possibility of local injection to treat a localized bacterial infection, such as periodontal disease.

Sampathkumar is cited for the proposition that periodontal disease is caused by bacterial infection. Applicant reiterates that knowledge that periodontal disease may be caused by bacteria does not, in and of itself, cure the deficiencies of the combination of Grabstein and Grzybowski. Moreover, the disclosure of Sampathkumar would not motivate one ordinary skilled in the art to modify Grabstein or Grzybowski *et al.* to arrive at the presently pending methods. Indeed, in order to arrive at the presently pending methods, one ordinary skilled in the art rather would need to:

- 1) Hope that GM-CSF would be effective against the anaerobic bacteria causing periodontal disease; and
- 2) Hope that a local administration of GM-CSF actually would have an effect on the bacterial infection.

One of ordinary skill in the art, upon reading the disclosures of Grabstein, Grzybowski *et al.*, and Sampathkumar, simply would not be motivated to combine the disclosures of the two references.

In summary, Grabstein only relates to systemic treatment, and there is no teaching or suggestion in that document as to how a formulation for local administration would be constituted. Grzybowski *et al.* fail to show that wound dressings containing GM-CSF have any function *in vivo*. Moreover, even assuming arguendo that the GM-CSF wound dressing have *in vivo* activity, such dressings are not suitable for oral, injectable use. Grzybowski *et al.* provide no teaching or suggestion on alternative ways of formulating GM-CSF for local administration by injection in the treatment of periodontal disease. Sampathkumar is cited merely for the proposition that periodontal disease is caused by bacterial infection. Sampathkumar, however, fails to provide any motivation for modifying the teachings of Grabstein, Grzybowski *et al.*, or itself, and certainly provides no guidance on how to achieve a method of treating periodontal disease by local injection of GM-CSF.

Even assuming arguendo that the combination of Grabstein, Grzybowski *et al.*, and Sampathkumar would result in the presently claimed methods, an assumption Application does not concede, in the absence of a motivation to combine the teachings of Grabstein, Grzybowski *et al.*, or Sampathkumar, the presently claimed methods cannot be obvious.

#### Reasonable Expectation of Success

As is known in the art, however, different administration routes often result in different effects. In the Request for Continued Examiner filed May 19, 2009, Applicant cited an article by Zhang *et al.* demonstrating that administering insulin locally results in a different side effect profile than systemic administration. Applicant also would like to draw the Examiner's attention to the Wikipedia page on "Routes of Administration." A print out of this page as it was published on September 13, 2009 is provided with the attached Information Disclosure Statement.

As explained in the introduction section of the Wikipedia page, "A route of administration in pharmacology and toxicology is the path by which a drug, fluid, poison, or other substance is brought into contact with the body. A substance must be transported from the

site of entry to the part of the body where its action is desired to take place (even if this only means penetration through the stratum corneum into the skin). Using the body's transport mechanisms for this purpose, however, is not trivial. The pharmacokinetic properties of a drug (that is, those related to processes of uptake, distribution, and elimination) are critically influenced by the route of administration." (emphasis added).

The "Uses" section specifies that "On the other hand, identical drugs can produce different results depending on the route of administration. For example, some drugs are not significantly absorbed into the bloodstream from the gastrointestinal tract and their action after enteral administration is therefore different from that after parenteral administration. This can be illustrated by the action of naloxone (Narcan), an antagonist of opiates such as morphine. Naloxone counteracts opiate action in the central nervous system when given intravenously and is therefore used in the treatment of opiate overdose. The same drug, when swallowed, acts exclusively on the bowels; it is here used to treat constipation under opiate pain therapy and does not affect the pain-reducing effect of the opiate." (emphasis added).

The above passages clearly support the point that simply demonstrating that GM-CSF can treat bacterial infections when administered systemically, as reported in Grabstein, in no way means that a similar effect will be obtained when GM-CSF can be used to treat anaerobic infections when administered locally. As noted above, Grzybowski *et al.* disclose a single method of local administration (a CSF-infused wound dressing) in the treatment of wound healing in mice. Importantly, Grzybowski *et al.* fail to demonstrate that wound dressings infused with the CSF of the pending claims, GM-CSF, have any *in vivo* effect on a bacterial infection.

Moreover, as described above, the bacteria treated in Grzybowski *et al.* are aerobic. In contrast, the bacteria causing periodontal disease, the subject of the presently pending claims, are anaerobic. One of ordinary skill in the art would have no reasonable expectation of success that such disparate bacterial infections could be successfully treated, particularly when Grzybowski *et al.* fail to provide any evidence that GM-CSF even works to treat aerobic bacteria.

In summary, one of ordinary skill in the art would have no expectation that the results achieved by Grabstein with systemic administration of GM-CSF could be recapitulated when treating periodontal disease by local injection of the molecule. Similarly, one of ordinary skill in the art would have no reason to expect that the untested GM-CSF containing wound dressings of

Grzybowski *et al.*, who were focused on aerobic bacteria and wound healing, could be successfully modified for local injection in the treatment of periodontal disease caused by anaerobic bacteria. Sampathkumar fails to disclose GM-CSF, and is silent on the subject of injection as a method of administration. As such, the disclosure of Sampathkumar does not provide one of ordinary skill in the art any further reason to expect that treating periodontal disease by local administration of GM-CSF would be successful.

In the absence of a reasonable expectation of success, the presently claimed methods cannot be obvious.

Calcification

Newly added claim 37 recites a method for inducing tooth calcification in a mammal, comprising locally administering by injection a therapeutically effective amount of a composition comprising at least one granulocyte-macrophage-colony stimulating factor (GM-CSF) polypeptide. Newly added claims 38-48 depend directly or indirectly from claim 37.

These claims are newly added and thus have not been rejected on the basis of Grabstein, Grzybowski *et al.* or Sampathkumar. Applicant notes, however, that none of these references, either alone or in combination, disclose or suggest that GM-CSF may be used to induce tooth calcification in a mammal. As such, none of Grabstein, Grzybowski *et al.* or Sampathkumar anticipates or renders obvious the methods of newly added claims 37-48.

Applicant submits that the present application is in condition for allowance, and respectfully requests a notice to that effect. If the Examiner feels that a telephone call would further prosecution or expedite allowance of the present case, the undersigned can be reached at 612-766-2071.

Please charge all required fees, and credit any overpayments, to deposit account 06-1050, referencing Attorney Docket No. 15665-0010US1.

Applicant : Henrik Arnberg  
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Respectfully submitted,

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/Cameron M. Luitjens/

Cameron M. Luitjens, Ph.D., J.D.  
Reg. No. 58,674

Fish & Richardson P.C.  
3200 RBC Plaza  
60 South Sixth Street  
Minneapolis, Minnesota 55402  
Telephone: (612) 335-5070  
Facsimile: (877) 769-7945

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